



Australian Government

Department of Health

Therapeutic Goods Administration

Regulation of autologous cells and tissues

Dr Ian Prosser
Senior Medical Adviser, Biological Science Section
Scientific Evaluation Branch, TGA
International Society for Cellular Therapy
Australia and New Zealand Regional Meeting

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TGA Health Safety
Regulation

Therapeutic Goods Administration (TGA)

- A division of the Australian Government Department of Health
- Regulates the safety, quality and efficacy of therapeutic goods in Australia
- Regulates medicines, devices, biologicals and blood
- Operates under cost recovery arrangements





How products are regulated

Therapeutic use/clinical trial products in humans

- Regulated by TGA
- *Therapeutic Goods Act 1989*

Food

- Regulated by Food Standards Australia New Zealand
- *Australia New Zealand Food Standards Code*

Research (potential therapeutic) products

- Research process regulated by the National Health and Medical Research Council
- *Australian Code for the Responsible Conduct in Research*
- Australian Health Ethic Committee Regulated by Pharmacy Board of Australia

Veterinary medicine

- Regulated by Australian Pesticides & Veterinary Medicines Authority
- *Agricultural and Veterinary Chemicals Act 1994*

Cosmetics & chemicals

- Regulated by National Industrial Chemicals Notification and Assessment Scheme
- *Industrial Chemical (Notification and Assessment) Act 1989*

Medical practice derived products

- Regulated by Medical board of Australia/Australian Health Practitioner Regulatory Agency
- *Health Practitioner Regulation National Law, National Registration and Accreditation Scheme*



What's in & what's out

Not regulated by the TGA

Assisted reproductive technologies
(in vitro fertilisation)

Fresh viable organs

Fresh hematopoietic progenitor cells
(bone marrow transplants)

Cells and tissues made by
a medical practitioner for
a single patient under the care
of that medical practitioner

Regulated as biologicals

Human stem cells

Tissue-based products
(skin, bone, ocular, cardiovascular)

Cell-based products
(genetically modified,
in vitro cell expansion/depletion)

Combined cell and
tissue products
(collagen matrices for localised
cell delivery)

Regulated, but not as biologicals

Biological prescription medicines
(vaccines, plasma derivatives)

Animal tissue products
(xenotransplantation)

Labile blood and blood components

Haematopoietic progenitor cells
(non-fresh transplants)

Exemptions under the Biologicals framework

- Non-viable **tissues of animal origin** e.g. porcine heart valves
- **Fresh viable human organs** for direct donor-to-host transplantation
- Fresh viable human **haematopoietic progenitor cells for direct donor-to-host transplantation** (e.g. bone marrow cells, cord blood)
- **Reproductive tissue** (e.g. sperm, eggs, embryos) that have not been processed in any way apart from freezing
- **Autologous tissue and cells**
 - collected from a patient **under the care of a medical practitioner, and**
 - manufactured for therapeutic treatment of a **single indication, and**
 - in a **single course of treatment** of that patient **by the same medical practitioner**, or by a person under their supervision
- **Other Autologous uses** are not exempt in Australia

Medical practice and therapeutic product regulation intersect

- Different regulatory frameworks oversee **medical practice** (Medical Board of Australia/ AHPRA) and **therapeutic products** (TGA), but the boundaries can overlap
- Concerns may also arise under the **Australian Consumer Law** where consumers are misled or deceived into believing that certain treatments are safe or effective when that is not the case
- Some **autologous** cell products are **excluded from TGA regulation under the Therapeutic Goods (Excluded Goods) Order 1 of 2011 under certain conditions**



Why have an Excluded Goods Order?

Some products have been declared not to be therapeutic goods and thus not regulated by TGA as a result of:

- **government policy** and to reflect Australian Health Ministers Advisory Council decisions
 - e.g. assisted reproductive therapy, fresh haematopoietic progenitor cells and organs for direct transplantation
- **alternative regulatory pathways apply**
 - self-regulation for assisted reproductive therapy
 - NPAAC guidelines and NATA accreditation for haematopoietic stem cell programs
 - Organ and Tissue Authority requirements for organ transplantation
 - **Medical practice**



Excluded Goods Order No.1 of 2011

Goods that are not treated by the TGA as coming within the regulatory framework created by the *Therapeutic Goods Act 1989* (the Act) and Regulations:

- o. fresh viable organs, or parts of human organs, for direct donor-to-host transplantation and used in accordance with applicable laws and standards;
- p. fresh viable human haematopoietic progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution;
- r. reproductive tissue for use in assisted reproductive therapy.



Excluded Goods Order No.1 of 2011

- q. human tissue and cells that are:
 - i. collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory;
- and**
- i. manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner



Excluded Goods Order

Key considerations

- Autologous cells and tissues only
- Patient under the care of the same registered medical practitioner
- Collection, 'manufacture' and application of cells or tissues under professional supervision of that medical practitioner
- Single course of treatment and indication
- Responsibility



Clinical procedures/treatments potentially within the current Item 4(q) exclusion

Autologous

- Skin grafts
- Skull flaps
- Vascular conduits
- Pancreatic islet cells
- Bone grafts
- HPCs for reconstitution of blood after treatment for cancer
- Blood components
- Cosmetic/reconstructive procedures (bone, skin and fat transfers)
- Autologous stem cells

Excluded Goods Order

Other considerations

- Standards relating to professional performance and advertising - regulated by APHRA
- Professional obligations of medical practitioners to maintain satisfactory standards of practice
- Whether the treatment being undertaken is necessary and safe and if efficacy is supported by credible clinical evidence
- Provision of adequate information to patients to enable them to give informed consent to treatment
- Regulation of advertising including under the provisions of the *Competition and Consumer Act 2010*
- Equipment and materials that are used for the manufacture of the product may still be therapeutic goods subject to regulation by the TGA

Concerns with the current regulatory model

- **Lack of evidence to support the efficacy** of some autologous cell therapies
- Large sums of money being charged for **unproven treatments**
- **Safety of some stem cell products** – either direct safety impacts or safety issues incidental to the therapy such as mode of collection or delivery
- **Lack of mechanisms** for reporting of adverse effects of the products
- **Inappropriate advertising** of the products



Understanding of risks of cell therapies is limited

- **Can risk of infectious disease transmission ever be eliminated?**
 - Cells and tissues often cannot be sterilised fully
 - Donor screening – difficult to obtain complete history for deceased donors
 - Subjective nature of exclusion decisions
 - Evolving knowledge e.g. prions and degenerative neurological diseases
- Many biologicals **cannot be stopped or removed** once in a recipient's body
- **Limited adverse event reporting** because only some stem cell therapies are in formal clinical trials and adverse events can also be masked by poor prognosis of critically ill patients
- **Unforeseen reactions** have been reported
 - e.g. heart attack, severe thrombosis, encephalomyelitis, ectopic bone tissue

What are some other regulators doing?

FDA

- New guidances are more prescriptive about what defines ‘homologous use’ and ‘minimal manipulation’
- ‘Right to try’ movements also have momentum

Europe

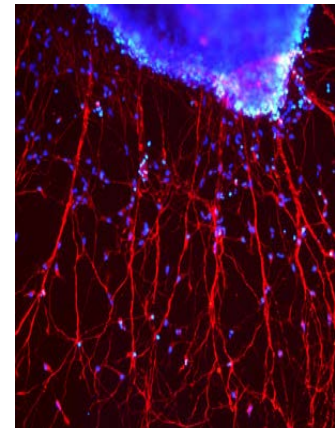
- Only about five ‘advanced therapy medicinal products’ have been approved by EMA
- ‘Hospital exemption system’ for some cell and tissue products rather than private clinics performing treatments

Japan

- ‘Provisional licensing’ system for cell therapies (SAKIGAKE initiative)
- Where initial safety and manufacturing results positive; limited term commercial licensing to establish product efficacy and confirm safety

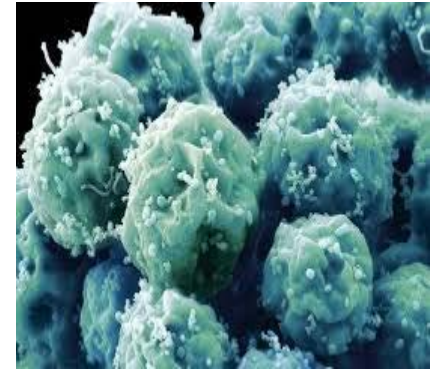
Is current Australian regulation of autologous stem cell appropriate ?

- Interpretation of ‘**minimally manipulated**’ and ‘**homologous use**’ is relevant
- **USFDA takes a narrow view** of ‘minimal manipulation’ and ‘homologous use’ for fat stem cells in Dec 2014 draft industry guidance documents
- In Australia, a **public consultation** (Jan-Mar 2015) was held to seek input on **five potential options for regulation** of these cells as therapeutic goods
- 80 submissions received



Next steps

- Cell and tissue regulation is a **new and evolving area** internationally
- **Response to the autologous stem cell consultation** will help inform what, if any, change is required to therapeutic goods regulation
- A second public consultation paper was released earlier this year, to seek further input into a number of regulatory options developed as a result of the first consultation in 2015
- 64 responses have been received and evaluation of these responses is now being undertaken



Part A proposed options

Characteristics of each Option	Option 1	Option 2	Option 3	Option 4
What autologous human cell and tissue products are excluded from TG Act regulation under options?				
Single medical/dental practitioner, single course of treatment and only minimal manipulation	Excluded from the <i>Therapeutic Goods Act 1989</i> (the Act)	Excluded from the Act	Excluded from the Act	Excluded from the Act
Single medical/dental practitioner, single course of treatment and greater than minimal manipulation	Excluded from the Act	Excluded from the Act	Not excluded from the Act but exempt from being on ARTG if single medical/dental practitioner and single course of treatment	Not excluded from the Act – regulated as Class 3 or 4 biological
Is advertising allowed?				
Direct advertising to consumers	Allowed	Not allowed under the exclusion	Not allowed under the exclusion	Not allowed under the exclusion
Regulatory outcome if not within exclusion for any reason				
	Regulated under the Act as a biological of whichever class is applicable (depends on reason not within exclusion).	Regulated under the Act as a biological of whichever class is applicable (depends on reason not within exclusion).	<p>If not within exclusion only because more than minimally manipulated then regulated under the Act as biological but:</p> <ul style="list-style-type: none"> • exempt from being on the ARTG; • must comply with standards and report adverse events; • notify TGA of new types; • subject to recall provisions; • no advertising. <p>If not within exclusion for any other reason then regulated under the Act as biological of whichever class is applicable (depends on reason not within exclusion).</p>	Regulated under the Act as biological of whichever class is applicable to the product (depends on reason not within exclusion)

Part A – discussion points

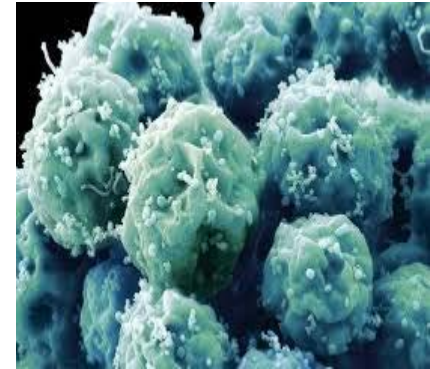
- **Scope - Human cell and tissue products for autologous use**
- **Under the supervision of a medical/**dental** practitioner**
- **As part of a single course of treatment vs single procedure**
- **Definition of minimal manipulation**
- **Homologous use**
- **Human cell and tissue products that form part of established medical practice**

Part B – consequential changes

- Current definition of minimal manipulation
 - *Minimal manipulation* is a process involving any of the following actions: centrifugation; trimming, cutting or milling; flushing or washing; refrigeration; freezing; freeze drying (of structural tissues only); the use of additives such as cryopreservatives, anticoagulants, antimicrobial agents; irradiation for the purpose of bioburden reduction; any other action that is similar to an action mentioned above.
- Proposed definition
 - *Minimal manipulation* is a process that does not result in alteration of the biological characteristics, physiological functions or structural properties relevant to the intended use.

Conclusions

- Cell and tissue regulation is a **new and evolving area** internationally
- **Response to the autologous stem cell consultation** will help inform what, if any, change is required to therapeutic goods regulation
- **Policy discussion** with Minister on options
- Determination of the **legal nature** of any change
- If any regulatory change is proposed a **Regulation Impact Statement (RIS)** would be required and undergo **further consultation**, including on costs and benefits to affected parties





More information

Therapeutic Goods (Excluded Goods) Order No. 1 of 2011

- <http://www.tga.gov.au/industry/legislation-excluded-goods-order-1101.htm>

Excluded Goods Order No. 1 of 2011: Guideline for items 4(o) – 4(r)

- <http://www.tga.gov.au/industry/legislation-excluded-goods-order-1101-guidance-4opqr.htm>

Further questions

- bloodandtissues@tga.gov.au